

**Antipsychotic Agents and Weight
Gain/Weight Loss: A review of the
Literature**

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Table of Contents

- 1.1 Measuring Obesity
- 1.2 Incidence and Prevalence of Obesity in the Schizophrenic Population
- 1.3 Effects of Antipsychotics on Neurotransmitters and Hormones that May Attribute to Obesity
- 1.4 Weight gain and Views on Therapy
- 1.5 Olanzapine and Weight Gain
- 1.6 Clozapine and Weight Gain
- 1.7 Risperidone and Weight Gain
- 1.8 Ziprasidone and Weight Gain
- 1.9 Management of Weight Gain
- 2.0 References

Introduction

Obesity strikes one in every three American adults (Center for Disease Control). Weight associated hypertension, type II diabetes, coronary heart disease, and stroke are just a few diseases sparking a growing concern for finding the root of weight gain. Atypical antipsychotics have been just one of the targets for weight gain especially among the schizophrenic population. The degree to which each atypical drug affects hormones and neurotransmitters, potentially linked to weight gain, is variable. Regardless of the weight gain effect, these drugs are a necessity to prevent schizophrenic relapse and improve the quality of life of a schizophrenic patient. The challenge now becomes to evaluate how each atypical agent correlates weight gain with clinical improvement and to prevent or manage patient's weight and potentially associated with life threatening diseases.

1.1 Measuring Obesity

The risks associated with overweight or obese individuals far exceeds exterior appearance, and the concern for weight gain has reached a new scientific high as 33% of adults in the United States are reported to be obese (Allison Nov. 1999). Reports indicate that a weight gain of five pounds or more within three years is a disruption in the body's appetite control and food ingestion (Blackburn 00). A good monitor of body fat is Body mass Index (BMI), which correlates relative weight (Kg) to height. The results of this equation will classify the patient into a specific category that relates to body fat (Blackburn 00).

Classification of Body Mass Index (BMI)

Body Mass Index	Classification
25-29.9	Overweight
>30	Obese
30-34.9	Class 1 (mild)
35-39.9	Class 2 (moderate)
>40	Class 3 (severe)

$$\text{BMI} = \text{Kg}/\text{m}^2$$

Secondly, waist circumference is a measure of fat in the abdomen and is an independent predictor of morbidity (Blackburn 00). Finally, everyone has an ideal body weight (IBW) based on sex and height. This measure is what an average person should weigh for their given height.

Men=(106lbs for the first 60 inches) + (6 lbs for each additional inch)
Women=(100lbs for the first 60 inches) + (5 lbs for each additional inch)
(Blackburn 00)

Classification of Ideal Body Weight (IBW)

Overweight	
Men	10% above IBW
Women	20% above IBW
Obese	
Men	35% above IBW
Women	45% above IBW

In a person of average body weight according to IBW, a weight increase of 5% of total body weight may increase morbidity and mortality associated with hypertension, type II diabetes, stroke and respiratory problems (Allison Nov. 1999). Obesity is a common societal problem that brings with it further complicating factors often overlooked or accepted by individuals.

1.2 Incidence and Prevalence of obesity in the schizophrenic population

There exists no direct data on how many obese patients have Schizophrenia, however, obesity may be a result of schizophrenia and related symptoms. Depression is an accompanying symptom of schizophrenia and may worsen upon progression of the illness resulting in a change of metabolic rate (Shiori 1993). The Epidemiologic Catchment Area study showed schizophrenic patients were 28.5 times more likely to have major depression than the general population (Keck 00). Many patients with primary depression or related depression show a loss of weight or are underweight upon admission. A recent study was aimed to characterize differences in body weight between individuals with and without schizophrenia (Allison April 1999). Results showed no significant difference in BMI of schizophrenic men versus healthy men. This result opposes women who have a high population of obese women with schizophrenia and a small percentage of underweight women (Allison April 1999). Schizophrenia, otherwise, shows no partiality to universal site, sex, or race. Onset of illness is usually after the age of 40 and may be seen earlier for men than women (Tasman 00). Studies have shown that people 45 years of age and unmarried have a three times greater chance of developing schizophrenia and poverty may be a result, as opposed to a contributing factor, of schizophrenia (Tasman 00).

1.3 Effects of antipsychotics on Neurotransmitters and Hormones that may attribute to obesity

Determining where obesity comes from can be clinically challenging because of patient variability when genes hormones and neurotransmitters are involved. The difference in Body Mass Index between men and women, described above, allows for the conclusion that hormones associated with gender does matter (Allison April 1999). Studies have shown that circulating levels of prolactin are correlated with BMI (Baptista 00). Externally detecting this hormone can be observed when weight is gained in the abdomen, due to insulin resistance causing fat accumulation (Baptista 00). Leptin is a hormone released by muscle and adipose tissue, it is partly responsible to homeostasis of metabolism and fat stores (Baptista 00). A study was conducted in mice and humans that indicated obesity when leptin levels are low and circulating leptin levels are increased (Kraus 99). However, food intake and weight were reduced upon administration of leptin. The question surrounding antipsychotics is whether or not leptin levels, weight gain, and antipsychotics are interrelated via cause and effect (Kraus 99). Serotonin and histamine are both common neurotransmitters that have been a target of antipsychotics (Wirshing 99). Food intake has been reported to decrease when serotonin (5-HT) has been administered (Wirshing 99), therefore, serotonin blocker would likely display an increase in food consumption. More specifically the 5-HT 2C receptor may be largely to blame for weight gain. Clozapine, risperidone and olanzapine all have affinity for the 5-HT 2C receptor, however, studies show that risperidone produced less weight gain (Wirshing 99). This study proved that serotonin blockade is not single handedly responsible for weight gain but in conjunction with histamine blockade, weight gain increased (Wirshing 99). Clozapine and olanzapine have this antihistamine component which may contribute to increase in food consumption and resulting weight gain.

1.4 Weight gain and views on therapy

Weight gain is a common side effect of many drugs. Therefore, if a patient is on a concurrent medication that causes weight gain, a synergistic or additive effect may be experienced. Such examples include antineoplastics, which averages an expected weight gain of 10 kg (Blackburn 00). Steroids are another common drug to average approximately 2 Kg during a six month treatment (Blackburn 00). Insulin and other diabetic medications show a weight increase of 2.6-5.1 Kg within the first year of treatment, where anticonvulsants average a mean gain of 21 Kg with valproate and tri-cyclic antidepressants causing a gain of 1.3-2.9 pounds per month of treatment (Blackburn 00). Weight gain may also be viewed as a positive step in recovery (Fava 00). Stimulation of the Dopamine-2 and the 5-HT-2C receptors have been associated with a decrease or no change in weight (Stahl 98), implying that weight loss may be a symptom of schizophrenia. Therefore, drug therapy is improving symptoms by increase in weight and appetite. Atypical depression may also feature increased appetite, carbohydrate craving and weight gain. A decrease

in appetite may indicate a decrease in depression as a result of medication. Typical depression associates more with weight loss during active depression and weight gain during treatment and improvement. Weight gain that continues despite achieving remission can be residual or side effects of medication, this diagnosis is very difficult to make (Fava 00). In a case of atypical depression, weight gain may indicate a noncompliant patient just as weight loss in typical depression. Regardless of the type of depression, monitoring and charting weight can be a helpful determinant in therapy protocol, and in recognizing a noncompliant patient (Blackburn 00).

1.5 Olanzapine and Weight Gain

Olanzapine is a chemical derivative of clozapine and therefore has inherited some of clozapine's traits. Both drugs are strong blockers of serotonin and histamine, which may set these two drugs apart from the rest (Osser 99). The specific weight gain mechanism is unknown at this time, however, it may secondary to the histamine-1 receptor blockade (Osser 99). If this were solely the case, it makes sense that olanzapine would be expected to cause predicted weight gain. Weight gain, as an element, is predictable, but to what extent can not be predicted for individual patients. Conley states that 56% of patients reported a weight gain of 7% of their starting body weight. The mean weight gain after one year of treatment was 11.8 kg while receiving a dose of 15, plus or minus, 2.5 mg/day. However, weight gain analysis during clinical trials showed that underweight patients prior to treatment with olanzapine were at the greatest risk of weight gain (Beasley 97), therefore having a greater percent change in weight. Although olanzapine has been associated with weight gain, there are several case reports on the use of olanzapine in cases of refractory psychosis (Reich99, Weiss 99). These cases present situations in which patients have been responsive to clozapine and could not tolerate adverse effects, or were nonresponsive to clozapine therapy. All of these patients were titrated to 50 mg of olanzapine and, were responsive to therapy and, all but one, were compliant with the medication regimen. Weiss reports reasons for relapse of one patient was due to noncompliance unassociated with adverse effects and that olanzapine was reinstated and the patient then stabilized. Even at high doses of olanzapine, weight gain did not affect patient compliance.

1.6 Clozapine and Weight Gain

Clozapine is an antipsychotic agent used in the treatment of schizophrenic patients (Lacy 2001). For many years weight gain has been a complaint of patients and a possible condition for noncompliance. In a case of 21 institutionalized patients with schizophrenia, non responsive to other antipsychotics, clozapine was administered (Ganguli 99). An average weight gain of 13.9 pounds was seen. In a case of unresponsive schizophrenia, changing the patient's antipsychotic medication may not be an option for the physician (Ganguli 99). Another small study compared 19 patients on clozapine versus 20 patients on haloperidol. The clozapine group had a gain of 7% over baseline weight. Over the first year of treatment, 58% of patients gained a minimum of 10 % over baseline where 21% gained, equal to or greater than, 20% of initial body weight (Bustillo 96). The controversy, however, is determining the correlation of weight gain to clinical improvement. Ganguli reports an inverse relationship, as opposed to Bustillo, reporting a significant correlation between weight gain and improvement on Brief Psychiatric Rating Scale (BPRS). The mechanism thought to cause weight gain in clozapine may be due to stronger antiserotonergic and antihistaminergic effects of (Bustillo 96). One case study had reported clozapine to induce or lower the seizure threshold causing a 29 year old male to have a seizure. topiramate was started and caused weight loss as well as mood stabilization when used in combination with clozapine (Dursun 97).

1.7 Risperidone and Weight Gain

Risperidone was the first atypical antipsychotic agent approved by the Food and Drug Administration for unrestricted use in Schizophrenia (Conley00). Risperidone lacks anticholinergic effects and is effective against positive and negative symptoms of schizophrenia (Conley 00). However, a meta analysis shows risperidone to be more effective for negative symptoms than haloperidol (Conley 00). A case study shows a seventeen year old male who presents with existing hallucinations and delusional thinking, uncontrolled with several neuroleptic agents, since the age of twelve. His weight upon beginning treatment was 74.5 kg.

The young boy returned home after becoming less paranoid and less hostile while on 4mg two times a day. His total weight gain during the seventeen months of treatment was 16.1 kg, placing the young male within the 90th percentile for weight with a BMI of 33.1 kg/m² (Kumra 97). Although risperidone does not have the highest incidence of weight gain, deterioration in clinical response has been reported in patients switched from clozapine therapy (Osser 99). Therefore, risk versus benefit must be considered when choosing an antineuroleptic agent.

1.8 Ziprasidone and Weight Gain

Ziprasidone is an atypical antipsychotic agent not yet on the market in the US. Its chemical structure is unrelated to any current antipsychotics (Keck 98). Ziprasidone has a high binding affinity for central 5HT-2A as well as central D2 receptors (Keck 98). Ziprasidone is an agonist of the 5-HT-1A receptor and an antagonist of 5-HT2C and 5-HT-1D while moderately inhibiting 5-HT (Tandon 00). Ziprasidone has low to modest affinity for the cholinergic and histamine receptors respectively (Tandon 00). Out of 139 patients enrolled in a four week placebo controlled trial of Ziprasidone, 107 (77%) experienced an adverse event (Keck 98). Among the higher incidence effects include, dyspnea, nausea, constipation, abdominal pain, EPS, coryzal symptoms and rash (Keck 98). Although no dose relationship was reported, elevated cholesterol and triglycerides were reported in over 20% of the patients in each treatment group (Keck 98). Only about 50% of patients on 120 mg/day completed the trial as opposed to 64% who finished on 40 mg/day (Keck 98). Insufficient response was stated to be the main clinical reason for noncompletion (Keck 98). This particular study did not mention weight gain or loss while on ziprasidone. (However, a case report of a 22 kg weight gain was seen-currently being written up as a case report, verbal communication from Patrick Jonsson).

1.9 Management of weight gain

Appearing that weight gain in antipsychotic therapy is a fixed complication, a turn towards management is becoming imperative. Candidates gaining greater than five pounds while on antipsychotic therapy are top priority for preventative treatment. First, the clinician must perceive how a patient views diet and exercise. Increasing patient knowledge of the dangers of excessive weight gain can be pivotal for adherence to any regimen. A strategy can then be installed utilizing nonpharmacological and psychopharmacological interventions first while monitoring speed of weight gain as well as progression from mild to severe. Consider pharmacotherapy after six months of unsuccessful weight maintenance through lifestyle and behavioral therapy (Blackburn 00) As demonstrated above, each antipsychotic plays a tremendous clinical importance in treatment of patients with both responsive and refractory psychosis. Due to patient variability, each patient tolerates these agents differently. Weight gain may be a small compromise for clinical improvement in the schizophrenic patient and the main solution is counseling the patient and the care giver of effects and benefits of these agents.

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